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| <b>Institution: Liverpool School of Tropical Medicine (LSTM)</b>   |  |  |
| <b>Unit of Assessment: UOA1</b>  |  |  |
| <b>Title of case study: Reducing the disease burden of tropical snakebite</b>  |  |  |
| <b>Period when the underpinning research was undertaken: 2000-2020</b>   |  |  |
| <b>Details of staff conducting the underpinning research from the submitting unit:</b>   |  |  |
| <b>Name(s):</b>  | <b>Role(s) (e.g. job title):</b>             | <b>Period(s) employed by submitting HEI:</b> |
| Rob Harrison   | Professor, Head of Venom Research Unit (VRU) | 1994 –                                       |
| Nick Casewell  | Professor, Deputy Head of VRU                | 2014 –                                       |
| David Laloo  | Professor of Tropical Medicine               | 1997 –                                       |
| David Theakston  | Professor, Past Head of VRU                  | 1970 – 2005                                  |
| <b>Period when the claimed impact occurred: 2014 – 2020</b>  |  |  |
| <b>Is this case study continued from a case study submitted in 2014? Y/<u>N</u> NO</b>   |  |  |
| <b>1. Summary of the impact</b> (indicative maximum 100 words)   |  |  |
| <p>Snakebite has historically been perhaps the most under-researched, under-resourced high mortality and high morbidity neglected tropical disease. The research and advocacy activities of Liverpool School of Tropical Medicine (LSTM) have impacted three key areas:</p> <ol style="list-style-type: none"> <li>defining the burden of and consequences of the problem, permitting increased funder and policymaker focus on snakebite - this directly led to the World Health Organization (WHO) formally classifying snakebite as a priority Neglected Tropical Disease in 2017 and, in 2019, establishing a strategy (co-written by LSTM scientists) to halve the global snakebite mortality and morbidity by 2030;</li> <li>design and implementation of a model intervention program, ensuring the delivery of significantly improved snakebite therapies (antivenoms) to countries in West Africa – this resulted in new, cost-effective, life-saving treatments;</li> <li>securing the supply of quality antivenoms by developing a 'prequalification' programme for ensuring the quality of snakebite therapeutics for Africa; this in turn has resulted in direct commercial impact for antivenom manufacturers.</li> </ol>  |  |  |
| <b>2. Underpinning research</b> (indicative maximum 500 words)   |  |  |
| <p>Snakebite is a medical emergency and the world's most lethal neglected tropical disease. Snakebite predominately affects poor rural populations of the tropics and results in approximately 138,000 deaths and approximately 400,000 disabilities per annum. Snakebite has long been neglected by funders and policy makers, which has resulted in only limited investment and funding. Studies led by LSTM have revealed the true burden of envenoming and have led to more efficacious, safer and affordable snakebite therapies.</p> <p>Impacts have been achieved in collaboration with the University of Kelaniya in Sri Lanka, the Nigerian Federal Ministry of Health and Bayero University of Kano, Nigeria and, more recently, from the 96+ researchers that LSTM has gathered for snakebite clinical and public health research in Nigeria, Kenya, eSwatini and India.</p> <p><b>Quantifying the burden of disease</b></p> <p>LSTM-led research has been central to the international effort to increase awareness of the substantial disease burden posed by snakebite worldwide. Laloo coordinated the highly influential publication estimating the global burden of snakebite, snakebite envenomings and snakebite deaths based on literature analysis and modelling [1]. Harrison and Laloo next demonstrated that snakebite is a disease of rural tropical poverty by evidencing clear associations between snakebite mortality and key economic and socioeconomic indices of</p> |  |  |

poverty [2]. Lalloo's later publication [3] was the first to demonstrate that snakebite also causes severe chronic psychological morbidity.

### Laboratory and Clinical Evaluation of Antivenoms

The EchiTab Study Group was established by LSTM and partners in 2006 and led by Theakston and Harrison as a response to the international crisis in the supply of effective antivenom for African snakebite victims, first highlighted by Theakston [4]. This collaboration of scientists, physicians, antivenom manufacturers and Nigerian Federal Ministry of Health representatives was funded by GBP1,920,000 from the Nigerian Federal Ministry of Health (between 2006 and 2012). The EchiTab study group focussed on mitigating snakebite mortality and morbidity in West Africa. Medically-important snakes were exported from Nigeria and housed at LSTM where research on the venoms was performed. LSTM designed and delivered venom mixtures for antivenom production by manufacturers in UK, Costa Rica, Egypt, Colombia and Mexico. LSTM then preclinically tested the efficacy of the resulting 5 antivenoms. Of these new antivenoms, 3 were submitted to (i) phase I clinical dose-finding and safety studies (resulting in the deletion of 1 product with an unacceptable safety profile) and (ii) a randomised controlled double-blind non-inferiority study of the remaining 2 antivenoms in Nigeria conducted between 2005 and 2007. This resulted in demonstrable efficacy and safety for both products [5], and remains the largest clinical trial undertaken on snakebite to date. Harrison and Casewell also demonstrated preclinical efficacy of these products against other snake species to which the antivenoms were not originally designed, thereby advocating for their broader clinical use across sub-Saharan Africa [6].

The initiation, funding, coordination, development, testing and delivery of the EchiTab antivenoms exemplifies LSTM's 'bench to bedside' research philosophy and capability. Other studies have been key in improving patient outcomes related to how antivenoms are used. Lalloo co-designed and ran a major clinical trial in partnership with the University of Kelaniya demonstrating that severe, potentially life-threatening, antivenom reactions could be decreased by 25% using adrenaline (epinephrine) prophylaxis [7].

### 3. References to the research (indicative maximum of six references)

1. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, Savioli L, **Lalloo DG**, de Silva HJ. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med. 2008. DOI: [10.1371/journal.pmed.0050218](https://doi.org/10.1371/journal.pmed.0050218)
2. **Harrison RA**, Hargreaves A, Wagstaff SC, Faragher B, **Lalloo DG**. Snake envenoming: a disease of poverty. PLoS Negl Trop Dis. 2009. DOI: [10.1371/journal.pntd.0000569](https://doi.org/10.1371/journal.pntd.0000569)
3. Williams SS, Wijesinghe CA, Jayamanne SF, Buckley NA, Dawson AH, **Lalloo DG**, de Silva HJ. Delayed psychological morbidity associated with snakebite envenoming. PLoS Negl Trop Dis. 2011. DOI: [10.1371/journal.pntd.0001255](https://doi.org/10.1371/journal.pntd.0001255)
4. **Theakston RD**, Warrell DA. Crisis in snake antivenom supply for Africa. Lancet. 2000. DOI: [10.1016/s0140-6736\(05\)74319-1](https://doi.org/10.1016/s0140-6736(05)74319-1)
5. Abubakar IS, Abubakar SB, Habib AG, Nasidi A, Durfa N, Yusuf PO, Larnyang S, Garnvwa J, Sokomba E, Salako L, **Theakston RD**, Juszczak E, Alder N, Warrell DA; Nigeria-UK EchiTab Study Group. Randomised controlled double-blind non-inferiority trial of two antivenoms for saw-scaled or carpet viper (*Echis ocellatus*) envenoming in Nigeria. PLoS Negl Trop Dis. 2010. DOI: [10.1371/journal.pntd.0000767](https://doi.org/10.1371/journal.pntd.0000767)
6. **Casewell NR**, Cook DA, Wagstaff SC, Nasidi A, Durfa N, Wüster W, **Harrison RA**. Pre-clinical assays predict pan-African *Echis* viper efficacy for a species-specific antivenom. LoS Negl Trop Dis. 2010. DOI: [10.1371/journal.pntd.0000851](https://doi.org/10.1371/journal.pntd.0000851)
7. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, Kalupahana R, Ratnatilaka GA, Uluwaththage W, Aronson JK, Armitage JM, **Lalloo DG**, de Silva HJ. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med. 2011. DOI: [10.1371/journal.pmed.1000435](https://doi.org/10.1371/journal.pmed.1000435)

**4. Details of the impact** (indicative maximum 750 words)**Positioning snakebite as a priority neglected tropical disease**

LSTM has been central to the international effort to increase awareness of the substantial disease burden posed by snakebite that culminated in the WHO recommendation that snakebite be listed as a priority neglected tropical disease. We organised highly influential international meetings that raised the global profile of snakebite, including the Wellcome-funded '*Mechanisms to reverse the public health neglect of snakebite victims*' 2015 meeting chaired by Harrison [1], and the 2016 Kofi Annan Foundation meeting, also organized and chaired by Harrison, in which Mr Kofi Annan declared snakebite as "*the biggest public health crisis you've never heard of*" [2]. In 2018, Casewell co-organised the Dutch Government funded "*Snakebite: from science to society*" international meeting that brought over 300 individuals (scientists, clinicians, pharmaceutical companies, public health practitioners, charities, policy makers, governments and funders) together to discuss solutions for tropical snakebite [3]. These meetings were instrumental in effecting change in international health policy. Initiatives resulting from this series of meetings include, WHO's 2018 listing of snakebite as a priority NTD (see below), the 2019 WHO strategy to halve snakebite mortality and morbidity by 2030 co-authored by Harrison and Lalloo [4] and Wellcome's 2019 investment of GBP80,000,000 in snakebite research.

The 2017 WHO recommendation that snakebite be listed as a priority neglected tropical disease was ratified by the World Health Assembly in 2018 [4] and has galvanised action from several governments. For example, the Kenya Ministry of Health NTD department has established a Snakebite Task Force, which includes a LSTM-research collaborator (Dr George Omondi) in its membership, and written national guidelines [5], that LSTM and its Kenya partners are delivering to hospitals and communities across Kenya. While awaiting full impact assessments, we have already observed increased hospital admission of snakebite victims (Kitui County) and demand for antivenom from Ministries of Health (Kitui & Baringo Counties).

LSTM has led many other advocacy activities that have improved global recognition of the public health burden posed by snakebite including advising and participating in numerous documentaries with a global reach between 2013 and 2019 for the BBC, BBC World, Discovery Channel, China Global Television Network, Natural History Museum and Royal Society for Tropical Medicine and Hygiene [6]. In particular, Harrison had extensive input into the development of a documentary with the Lillian Lincoln Foundation entitled "*Minutes to Die*" [6] which highlighted the plights of victims and the scientists seeking to redress the issue.

In 2018, LSTM was a main partner with the Royal Society of Tropical Medicine & Hygiene in the development of the inaugural International Snakebite Awareness Day. This initiative included participation from the Wellcome Trust, the Global Snakebite Initiative, Medecins Sans Frontiers, the Kofi Annan Foundation and Health Action International. Casewell and Harrison filmed a short documentary film on snakebite and contributed to the recording of BBC World visual and audio documentaries on snakebite in Kenya, both of which were used in the inaugural event in London [6]. Casewell's co-written opinion piece for the general public on the BBC News website in 2019 "Why are so many people still dying from snake bites?" [6] has been viewed over 500,000 times.

**Improving snakebite therapies**

The EchiTAb Study Group activities resulted in the development of two new, efficacious, safe and cost-effective antivenoms that received National Marketing Authorisations from the Nigerian National Agency for Food and Drug Administration and Control (NAFDAC), in 2005 [7]. A two year evaluation on the impact of the introduction of these antivenoms into Nigeria, conducted between 2009 and 2010, found snakebite mortality decreased from 35-45% in the absence of antivenom to 1.52% after the venom was introduced [8]. In addition, the dose of antivenom required with the new therapeutics was decreased from 6 vials to between 1 and 3 vials, compared with previous products [8], thereby also resulting in a decrease of at least 50% to the cost of treatment to impoverished victims and the health system. Our in-country partners indicate that these pre-REF 2021 efficacy, cost-effectiveness and mortality-reduction figures have

remained constant thereafter and the EchiTab antivenoms remain the standard of care in Nigeria and other countries (see below).

Our findings that adrenaline prophylaxis can reduce severe reactions to antivenom led to the routine recommendation of adrenaline prophylaxis in WHO guidelines in 2016 [9]; adrenaline is included as a strong recommendation in almost all national snakebite guidelines. The routine use of adrenaline prophylaxis has been reported to be associated with reduced mortality from snakebite; some clinicians avoided antivenom use because of their fear of reactions and being able to prevent or manage reactions using adrenaline increased the use of life-saving antivenom [10].

### Enabling access to antivenom

As a result of our advocacy on the need for quality assurance processes, WHO have established an 'antivenom prequalification' process, by which independent risk benefit analyses following robust laboratory assessment of available antivenoms are performed to ensure the quality of snakebite therapeutics for Africa [11]. The EchiTab Study Group-developed antivenom EchiTabG, manufactured by MicroPharm Limited, was the first product to receive WHO-approval via this process in 2019.

The EchiTab Study Group project also resulted in commercial and reputational benefits to the antivenom manufacturers. Thus, the SME, MicroPharm Limited (UK) benefitted from (i) 5 years investment in their production of EchiTabG, (ii) ownership of a brand that is now the standard snakebite treatment throughout Nigeria and neighbouring countries, and (iii) an Africa-antivenom production reputation that resulted in its selection to sustain the production/delivery of FavAfrique from Sanofi (2019/20). Similarly, based upon the success of its antivenom (EchiTab-Plus) in Nigeria, the Costa Rican antivenom manufacturer, Instituto Clodomiro Picado (ICP), is now distributing EchiTab-Plus to many other countries, including Burkina Faso, Mali, Ghana, Central African Republic and irregularly to other West African countries. While no formal epidemiological studies have quantified the impact this antivenom has had in these countries, the similar pattern of snake envenoming and well documented challenges with poor quality or non-availability of antivenom make it highly likely that there has been a decrease in mortality of at least 33%, as observed in north-east Nigeria [8]. The EchiTab Study Group project has since become recognised as a model for north-south and south-south collaboration for delivery of significantly improved snakebite therapies to tropical countries in greatest need [12]. Indeed, using the 'EchiTab' model, ICP has established similar new partnerships in Sri Lanka (~2014-2018) and Papua New Guinea (~2012-2016) to deliver new life-saving antivenom products to market in these resource-poor, high snakebite burden, areas [12].

## 5. Sources to corroborate the impact (indicative maximum of 10 references)

### Positioning snakebite as a priority neglected tropical disease

1. Publication: Harrison RA, Gutiérrez JM. Priority Actions and Progress to Substantially and Sustainably Reduce the Mortality, Morbidity and Socioeconomic Burden of Tropical Snakebite. Toxins (Basel). 2016. DOI: [10.3390/toxins8120351](https://doi.org/10.3390/toxins8120351)
2. Meeting report: Kofi Annan Foundation meeting on snakebite <https://www.kofiannanfoundation.org/combating-hunger/public-health-snakebite/>
3. Meeting report: Snakebite: from science to society. 2018
4. Strategy: World Health Organization. (2019) Snakebite envenoming: A strategy for prevention and control (Lalloo and Harrison co-authors). <https://apps.who.int/iris/bitstream/handle/10665/324838/9789241515641-eng.pdf>
5. Kenyan national guidelines, <https://kma.co.ke/Documents/Snakebite%20Envenoming%20in%20Kenya.pdf>
6. Documentaries: BBC World and Lillian Lincoln <https://www.youtube.com/watch?v=TKoQrXcDafc&fbclid=IwAR2Ob4kBATotAs03B5XpeDa4UeACqra5K3581ZynpAGaQlyG5XCb8E7Xnpg&app=desktop> and

<https://www.youtube.com/channel/UCrLPYxMWPLVAqCbho6Oy70Q> and  
<https://www.bbc.co.uk/news/world-45332002>

### Improving snakebite therapies

7. Website: Nigeria Drugs and Devices website for EchiTabG antivenom  
<https://rxnigeria.com/en/items?task=view&id=2639> and for EchiTab-Plus antivenom  
<https://rxnigeria.com/en/items?task=view&id=2640>
8. Publication: Ademola-Majekodunmi FO, Oyediran FO, Abubakar SB. Incidence of snakebites in Kaltungo, Gombe State and the efficacy of a new highly purified monovalent antivenom in treating snakebite patients from January 2009 to December 2010. Bull Soc Pathol Exot. 2012. DOI: [10.1007/s13149-012-0232-2](https://doi.org/10.1007/s13149-012-0232-2)
9. Guidelines for the management of snakebites, 2nd edition.  
<https://www.who.int/snakebites/resources/9789290225300/en/>
10. Statement on how use of adrenaline (epinephrine) prophylaxis has led to increased use of anti-venom in India. Bawaskar HS, Bawaskar PH. Snakebite envenoming. Lancet. 2019. DOI: [10.1016/S0140-6736\(18\)32745-4](https://doi.org/10.1016/S0140-6736(18)32745-4)

### Enabling access to antivenom

11. WHO Assessment and Listing of Antivenoms:  
[https://www.who.int/medicines/news/snake\\_antivenoms\\_assessment\\_listing/en/](https://www.who.int/medicines/news/snake_antivenoms_assessment_listing/en/)
12. Examples of Partnerships following the EchiTab model:  
**Papua New Guinea:** Gutiérrez JM. Understanding and confronting snakebite envenoming: The harvest of cooperation. Toxicon. 2016. DOI: [10.1016/j.toxicon.2015.11.013](https://doi.org/10.1016/j.toxicon.2015.11.013)  
**Sri Lanka:** Sri Lanka's antivenom leap forward  
<https://www.aljazeera.com/indepth/features/2017/02/sri-lanka-anti-venom-leap-170205103054069.html>